DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

m49650

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

DEC 14 2000

CBER 01-007

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Susan Hellman, M.D.
Executive Vice President,
Development and Product Operations, and
Chief Medical Officer
Genentech, Inc.
1 DNA Way
South San Francisco, California 94080-4990

Dear Dr. Hellman:

During an inspection of your facility located at 1 DNA Way, South San Francisco, California, from August 7 to 24, 2000, our investigators identified the following violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680:

1. Failure to submit a supplement and obtain approval prior to distribution of a product following any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, and potency of the product as they may relate to the safety or effectiveness of the product [21CFR 601.12(b)] in that, two Pulmozyme thawed bulk lots, G90536/PRK11930 and G90536/K14225, were re-filtered after brown foreign material and brown particulates were observed. Final vial lot K9721A was released by Quality Assurance and subsequently distributed.

2. Failure to obtain approval from the quality control unit prior to reprocessing [21 CFR 211.115(b)] in that, there is no documentation that the quality control unit was notified prior to the re-filtration of Activase lot #L9042A. On April 10, 2000, during set up for filling, manufacturing detected a leak in the connection during

during set up for filling, manufacturing detected a leak in the connection during priming. On April 11, 2000, the bulk was re-filtered by manufacturing and filled as Activase lot #L9046A.

3. Failure to follow or maintain written procedures and to record and justify any deviation from written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

   a. On January 15, 2000, during the manufacture of Pulmozyme bulk lot ———, an expired concentrated bulk ——— was used. There is no indication that the impact to material, which was held for an extended period of time, was evaluated.

   b. On April 29, 2000, lyophilizer ~ did not achieve the specified pressure during primary drying for Herceptin lot #L9047A. Partially stoppered product vials were stored ——— lyophilizer ~ Manufacturing personnel opened the ——— on April 29, 2000, and on May 1, 2000, to repair the door gasket miter joint. There is no documentation that the impact of product exposed at ——— in excess of the validated lyophilization cycle parameters was evaluated. In addition, during the inspection, evidence was not provided to indicate that a media fill that incorporated these interventions had been conducted.

   c. During the manufacture of Pulmozyme bulk lot ———, manufacturing personnel reduced the agitation rate from the specified ——— after the bulk began to foam. No justification was provided for choosing the alternate mixing speed or explanation of why foaming occurred.

4. Failure to conduct and document a thorough investigation of any unexplained discrepancy or failure of a batch to meet its specifications or extend the investigation to other batches that may have been associated with the specific failure or discrepancy [21CFR 211.192]. For example:

   a. Incident Report ——— issued on April 24, 2000, stated that particulates were observed in the re-circulation tubing used to transfer thawed Pulmozyme (rhDNase) bulk ———. The particulates were identified as damaged rhDNase and stainless steel. During the inspection, justification was not provided to allow re-filtration of a bulk with particulates. In addition, there is no assurance that the reprocessing was performed after review and approval by the quality control unit.

   b. Brown foreign material and brown particulates were observed in Pulmozyme thawed bulks ———

Particulates from the re-filtered concentrated bulks were identified as cellulose and polyamide. There were no additional investigations conducted to determine the source of the cellulose and polyamide after re-filtration.

c. Blue-gray particulates were observed for Pulmozyme thawed bulk [redacted] The particulates in the bulk prior to dilution were identified as protein and stainless steel. At the completion of the dilution, dark particulates were observed during bulk sampling. The particulates observed in the diluted bulk were identified as cellulose. There was no additional investigation conducted to determine the source of the cellulose observed in the diluted bulk.

5. Failure to promptly notify the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any product [21CFR 600.14(a)]. For example:

a. Two Pulmozyme thawed bulk lots, [redacted], were re-filtered after brown foreign material and brown particulates were observed. Final vial lot K9721A was released by Quality Assurance. However, there is no approved standard operating procedure (SOP) to allow for re-filtration due to particles and the incident was not reported to the agency.

b. Blue-gray particulates were observed in Pulmozyme thawed bulk lot [redacted] The bulk was released for filtration. Final vial lot K9720A was released by Quality Assurance. However, there is no approved SOP to allow for re-filtration due to particles and the incident was not reported to the agency.

We acknowledge receipt of your responses dated September 8, October 13 and 20, 2000, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

2b1. The response dated October 20, 2000, states that the Herceptin lot "did not fail a specification, rather, an in-process control limit was not met." Please ensure that investigations address why validated processes fail when following standard procedures.

3. The response dated October 13, 2000, states that a Single Discrepancy System will be implemented. The documents submitted by investigators with the inspection report refer to observations, manufacturing variances, laboratory variances, Good Manufacturing Practice incidents, incident reports, discrepancies, product quality investigations, manufacturing holds, action limit excursions, out of trend results, initial out of specification results, anomalous results, failures, non-conforming material reports, and material review board reports. Please indicate which of the above are separate systems for tracking problems and which of these old systems will be replaced by the new Single Discrepancy System. In addition, please describe how the new Single Discrepancy System will enable you to determine whether a variance at an early stage of the process, i.e., fermentation is related to an anomalous test result at a later stage, i.e., finished product testing.

8. We acknowledge your commitment to remove from production column C1130 which began to show corrosion. We note that the SOP entitled, "Pressure Vessel Corrosion Evaluation," page 3, states, in part, that if corrosion of a tank is found, then "remove tank from service and repair before returning to production." Should corrosion be detected at or near the end of a production campaign, product manufactured in the tank should be evaluated to ensure that identity, strength, quality, and purity have not been altered.

   During the October 4, 2000, meeting between representatives from Genentech, Inc., and the Food and Drug Administration (FDA), you discussed several steps intended to ensure the suitability of materials used in construction of equipment. You stated that the [redacted] column would be replaced with a stainless column that would provide greater corrosion protection. In addition, you indicated that currently [redacted] and that tanks and columns would be evaluated for corrosion as they became available and replaced, as appropriate. If corrosion is detected in tanks or on columns, product should be evaluated to ensure that identity, strength, quality, and purity have not been altered.

The responses dated October 13 and 20, 2000, for items 2, 4, 5, 6, 8, and 9 state that revised SOPs, testing procedures and new SOPs will be submitted to the FDA. Please note that it is not necessary to submit these procedures as all documents will be reviewed during the next inspection.

Observation numbers 2a1, 2a2, 2b2, 3a, 3b, and 4e3 describe deviations from written manufacturing procedures or from batch record instructions. Investigations should contain documented assessments as to whether deviations from written procedures are within the validated parameters. We noted during our evaluation of the investigations for these items that review of process validation was not addressed or documented. In addition, some of the investigations concluded that there was no adverse effect on the product because the batches passed routine laboratory testing. Routine sampling and test procedures are established based on the understanding that manufacturing will be in

accordance with validated processing parameters. When validated processing parameters are not followed, it may be necessary to consider additional testing to verify the acceptability of products.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the FD&C Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction, and/or civil penalties.

You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-600, Suite 200N, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Sincerely yours,

Deborah D. Ralston
Director
Office of Regional Operations

cc: Art Levinson, Ph.D.
Chairman and Chief Executive Officer